

We Claim:

1. A method of forming a coating on a surface of a medical device, the coating imparting improved biocompatibility characteristics to the surface, the method comprising the steps of:

(a) providing the medical device, the device having a biomaterial disposed on or forming a surface thereof, the biomaterial comprising an unsubstituted amide moiety;

(b) combining the amide moiety with an amine forming agent to form an amine-functional surface;

(c) providing a biomolecule, the biomolecule comprising a chemical moiety selected from the group consisting of an aldehyde moiety formed by combining a periodate with a 2-aminoalcohol moiety, an aldehyde moiety formed by combining a periodate with a 1,2-dihydroxy moiety, an epoxide moiety, an isocyanate moiety, a 1,2-dicarbonyl moiety, a phosphate moiety, a sulphate moiety and a carboxylate moiety; and

(d) combining the chemical moiety with the surface to form a chemical bond, the chemical bond immobilizing the biomolecule on the surface, the immobilized biomolecule forming the coating.

2. The method of claim 1 wherein the device is selected from the group consisting of a blood-contacting medical device, a tissue-contacting medical device, a bodily fluid-contacting medical device, an implantable medical device, an extracorporeal medical device, a blood oxygenator, a blood pump, tubing for carrying blood, an endoprosthesis medical device, a vascular graft, a stent, a pacemaker lead, a heart valve, temporary intravascular medical device, a catheter and a guide wire.

3. The method of claim 1 wherein the biomaterial comprises an amino acid residue.

4. The method of claim 1 wherein the amine forming agent is selected from the group consisting of bromine, bromide, bromite, hypobromite, chlorine, chloride, chlorite, hypochlorite, lead tetraacetate, benzyltrimethylammonium tribromide, [bis(trifluoroacetoxy)iodo]benzene, hydroxy(tosyloxy)iodobenzene and iodosylbenzene.

5. The method of claim 1 wherein the biomolecule is selected from the group consisting of an anticoagulant agent, an antithrombotic agent, a clotting agent, a platelet agent, a blood agent, an anti-inflammatory, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a regulatory agent, a transport agent, a fibrous agent, a protein, avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein, a cell attachment protein, a peptide, a glycopeptide, a structural peptide, a membrane peptide, a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, antibacterial agent, antimicrobial agent, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a lectin, a dye and a ligand.

6. The method of claim 1 wherein the biomolecule is a naturally occurring biomolecule.

7. The method of claim 1 wherein the biomolecule is a chemically synthesized biomolecule.

8. The method of claim 1 wherein the biomolecule comprises an amino acid residue.

5 9. The method of claim 1 wherein the periodate comprises at least one of a periodic acid, a sodium periodate, an alkali metal periodate, and a potassium periodate.

10 10. The method of claim 1 comprising the further step of combining at least one reducing agent selected from the group consisting of sodium borohydride, sodium cyanoborohydride and amine borane.

15 11. The method of claim 1 comprising the further step of combining the amine-functional surface with a guanidino forming agent to form a guanidino-functional surface.

12. The method of claim 11 comprising the further step of combining a stabilizing agent.

20 13. The method of claim 12 wherein the stabilizing agent is a borate ion.

25 14. The method of claim 11 wherein the guanidino forming agent is selected from the group consisting of S-ethylthiuronium bromide, S-ethylthiuronium chloride, O-methylisourea, O-methylisouronium sulfate, O-methylisourea hydrogen sulfate, S-methylisothiurea, 2-methyl-1-nitroisourea, aminoiminomethanesulfonic acid, cyanamide, cyanoguanide, dicyandiamide, 3,5-dimethyl-1-guanylpurazole nitrate and 3,5-dimethylpyrazole.

15. The method of claim 1 wherein at least a portion of the surface forms at least one of a tube, a rod, a membrane, a balloon, a bag, a sheet, a string, a suture, a fiber and a mesh.

5 16. The method of claim 1 wherein the surface comprises at least one of a biocompatible material selected from the group consisting of a metal, titanium, titanium alloy, tin-nickel alloy, a shape memory alloy, aluminum oxide, platinum, platinum alloy, stainless steel, MP35N stainless steel, elgiloy, stellite, pyrolytic carbon, silver carbon, glassy carbon, polyamide,
10 polycarbonate, polyether, polyester, polyolefin, polyethylene, polypropylene, polystyrene, polyurethane, polyvinylchloride, polyvinylpyrrolidone, silicone elastomer, fluoropolymer, polyacrylate, polyisoprene, polytetrafluoroethylene, rubber, ceramic, hydroxapatite, human protein, human tissue, animal protein, animal tissue, bone, skin, tooth, collagen, laminin, elastin, fibrin, wood,
15 cellulose, compressed carbon and glass.

17. A method of forming a coating on a surface of a medical device, the coating imparting improved biocompatibility characteristics to the surface, the method comprising the steps of:

20 (a) providing the medical device, the device having a suitable biomaterial disposed on or forming a surface thereof, a chemical moiety being disposed on the surface, the chemical moiety being selected from the group consisting of an aldehyde moiety, an epoxide moiety, an isocyanate moiety, a 1,2-dicarbonyl moiety, a phosphate moiety, a sulphate moiety and a
25 carboxylate moiety;

(b) providing a biomolecule, the biomolecule comprising an unsubstituted amide moiety;

(c) combining the amide moiety with an amine forming agent to form an amine-functional biomolecule; and

(d) combining the biomolecule with the surface to form a chemical bond, the chemical bond immobilizing the biomolecule on the surface, the immobilized biomolecule forming the coating.

5 18. The method of claim 17 wherein the device is selected from the group consisting of a blood-contacting medical device, a tissue-contacting medical device, a bodily fluid-contacting medical device, an implantable medical device, an extracorporeal medical device, a blood oxygenator, a blood pump, tubing for carrying blood, an endoprosthesis medical device, a vascular graft,
10 a stent, a pacemaker lead, a heart valve, temporary intravascular medical device, a catheter and a guide wire.

19. The method of claim 17 wherein the biomaterial comprises an amino acid residue.

15 20. The method of claim 17 wherein the aldehyde moiety is formed by combining a periodate with a 2-aminoalcohol moiety.

21. The method of claim 17 wherein the aldehyde moiety is formed by
20 combining a periodate with a 1,2-dihydroxy moiety.

22. The method of claim 17 wherein the periodate comprises at least one of a periodic acid, a sodium periodate, an alkali metal periodate, and a
25 potassium periodate.

23. The method of claim 17 wherein the biomolecule is selected from the group consisting of an anticoagulant agent, an antithrombotic agent, a clotting agent, a platelet agent, a blood agent, an anti-inflammatory, an antibody, an antigen, an immunoglobulin, a defense agent, an enzyme, a hormone, a growth factor, a neurotransmitter, a cytokine, a regulatory agent, a transport agent, a fibrous agent, a protein, avidin, a glycoprotein, a globular protein, a structural protein, a membrane protein, a cell attachment protein, a peptide, a glycopeptide, a structural peptide, a membrane peptide, a cell attachment peptide, a proteoglycan, a toxin, an antibiotic agent, antibacterial agent, antimicrobial agent, a polysaccharide, a carbohydrate, a fatty acid, a catalyst, a drug, biotin, a vitamin, a DNA segment, a RNA segment, a nucleic acid, a lectin, a dye and a ligand.

24. The method of claim 17 wherein the biomolecule is a naturally occurring biomolecule.

25. The method of claim 17 wherein the biomolecule is a chemically synthesized biomolecule.

26. The method of claim 17 wherein the biomolecule comprises an amino acid residue.

27. The method of claim 17 wherein the amine forming agent is selected from the group consisting of bromine, bromide, bromite, hypobromite, chlorine, chloride, chlorite, hypochlorite, lead tetraacetate, benzyltrimethylammonium tribromide, [bis(trifluoroacetoxy)iodo]benzene, hydroxy(tosyloxy)iodobenzene and iodosylbenzene.

28. The method of claim 17 comprising the further step of combining at least one reducing agent selected from the group consisting of sodium borohydride, sodium cyanoborohydride and amine borane.

5 29. The method of claim 17 comprising the further step of combining the amine-functional biomolecule with a guanidino forming agent to form a guanidino-functional biomolecule.

10 30. The method of claim 29 comprising the further step of combining a stabilizing agent.

31. The method of claim 30 wherein the stabilizing agent is a borate ion.

15 32. The method of claim 29 wherein the guanidino forming agent is selected from the group consisting of S-ethylthiouronium bromide, S-ethylthiouronium chloride, O-methylisourea, O-methylisouronium sulfate, O-methylisourea hydrogen sulfate, S-methylisothiourea, 2-methyl-1-nitroisourea, aminoiminomethanesulfonic acid, cyanamide, cyanoguanide, dicyandiamide, 3,5-dimethyl-1-guanylpurazole nitrate and 3,5-dimethyl
20 purazole.

33. The method of claim 17 wherein at least a portion of the surface forms at least one of a tube, a rod, a membrane, a balloon, a bag, a sheet, a string, a suture, a fiber and a mesh.

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34. The method of claim 17 wherein the surface comprises at least one of a biocompatible material selected from the group consisting of a metal, titanium, titanium alloy, tin-nickel alloy, a shape memory alloy, aluminum oxide, platinum, platinum alloy, stainless steel, MP35N stainless steel, elgiloy, stellite, pyrolytic carbon, silver carbon, glassy carbon, polyamide, polycarbonate, polyether, polyester, polyolefin, polyethylene, polypropylene, polystyrene, polyurethane, polyvinylchloride, polyvinylpyrrolidone, silicone elastomer, fluoropolymer, polyacrylate, polyisoprene, polytetrafluoroethylene, rubber, ceramic, hydroxapatite, human protein, human tissue, animal protein, animal tissue, bone, skin, a tooth, collagen, laminin, elastin, fibrin, wood, cellulose, compressed carbon and glass.